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PATENT
Attorney Docket No.: 15280W-003000
Client Ref. No.: E-155-99/0

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Hyun K. Kim, *et al.*

Application No.: 09/526,855

Filed: March 17, 2000

For: STRUCTURAL MODIFICATION OF 19-NORPROGESTERONE I: 17-α-SUBSTITUTED-11-β-SUBSTITUTED-4-ARYL AND 21-SUBSTITUTED 19-NORPREGNADIENEDIONE AS NEW ANTIPROGESTATIONAL AGENTS

Examiner: B. Badio

Art Unit: 1616

***Declaration of Hyun K. Kim. Ph.D. Under 37 C.F.R. § 1.132***

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Hyun K. Kim, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I am currently a Chemist in the Contraception and Reproductive Health Branch of the Center for Population Research at the National Institute of Child Health and Human Development, a division of the National Institutes of Health, Bethesda, Maryland. I have been with the NIH since 1972; prior to that, I was a Senior Research Scientist at Bristol Laboratoires in Syracuse, NY from 1970 to 1971; an Organic Research Chemist at Hess and Clark, a division of Richardson Merrell, Inc. in Ashland, OH during 1966-1969; and a Research Chemist at E.I. du Pont de Nemours and Col, in Parlin, NJ from 1965 to 1966.

3. I received a B.S. from Scoul National University in Seoul, Korea, where I was a University scholar, and received a Ph.D. in Medicinal Chemistry from the University of Michigan, under the late Dr. Fred F. Blicke. After that, I was a Postdoctoral Fellow at Vanderbilt University from June 1963 to July 1965. Attached hereto as Exhibit A is a true copy of my *curriculum vitae*.

4. I am a named inventor on the above-referenced patent application. I have read and am familiar with the contents of this patent application. In addition, I have read the Final Office Action, dated February 14, 2002, received from the United States Patent & Trademark Office in the above-referenced patent application. It is my understanding that the Examiner is concerned that (1) the compounds claimed are obvious in light of U.S. Patent No. 5,244,886 to Scholz, *et al.* (hereinafter Scholz), and (2) the compounds claimed are obvious in light of U.S. Patent No. 5,741,787 to Peeters, *et al.* (hereinafter Peeters). For the reasons set forth herein, the Examiner's concerns are overcome.

5. With respect to the Examiner's first concern, it is pointed out that a key limitation of Scholz that is *explicit* in the title, the description, and the claims distinguishes it from the compounds of the present invention. Sholz is directed to a genus containing a steroidal nucleus characterized by a 14-$\beta$-H stereocenter (hereinafter C-14), so the genus in Scholz specifically excludes the present invention. In my opinion, the 14-$\beta$-H feature is extraordinary in steroid compounds, and this is reflected in the Scholz patent, which states:

> As a special feature the compounds of this invention, deviating from naturally occurring steroids, exhibit a *beta*-position hydrogen atom on the 14 carbon atom. Such 14$\beta$-H steroids have already recently become known to a limited extent from European patent application 0 277 676.

U.S. Patent No. 5,244,886 to Scholz, *et al.*, column 2, lines 54-59.

6. The compounds of the present invention are of the 14-$\alpha$-H configuration, the opposite of that in Scholz, and they are thus not a subgenus of the 14-$\beta$-H compounds described in Scholz, in my opinion. Since 14-$\alpha$-H is the 'natural' configuration (*see id.*) it is not explicitly indicated in the generic structure of the present application. However, in my opinion, it is supported as being 14-$\alpha$-H by the naming of compounds throughout the application, and the 14-$\alpha$-H stereochemistry of these compounds would be readily understood by chemists skilled in steroid chemistry from the generic structure as it is drawn in the original application. Note, for example, that even in Scholz, none of the other ring fusion stereocenters is explicitly indicated: only the unnatural one is made explicit with a "wedge bond" in their structures.

7. Also note that this is true only for the ring fusion centers. Stereochemistry at other centers, notably C-17, must be explicitly designated, in my opinion, for a steroid chemist to understand the structure accurately.

8. The title of the present application names the compounds of the invention as substituted versions of norpregnadienedione. This is a common name that, in my opinion, conveys to one of ordinary skill in steroid chemistry that the stereochemistry at C-14 is 14-α-H, the natural configuration: if it were otherwise, that would be an unusual feature that would have to be explicitly indicated in order to be understood. By convention, the stereochemistry of the ring fusion stereocenters of a steroid compound is generally not designated unless it departs from the naturally occurring form. Like the common names used, the simplified structures are a well-understood shorthand among steroid chemists. For example, although they are chiral and optically active, no (+) or (-) optical rotation is indicated for the named steroids in this application or in Peeters or Scholz. Yet, in my opinion, the absolute stereochemistry at each ring fusion center is clearly understood to be the natural configuration *in the absence of a contrary indication*. In the above referenced application, therefore, the stereochemistry was not specifically designated in the compound recited in claim 1, but the name norpregnadienedione, like the names of the starting materials and intermediates in the examples (*cf.* Example 1, step 1 on page 20, naming a trimethylsilyloxyestra-5(10), 9(11)-diene), conveys the fact that the stereochemistry at C-14 is "14-α-H", the natural configuration.

9. Moreover, in my opinion, the biological activity of a steroid compound is so dependent on the stereochemistry of the ring fusion centers that, to a steroid chemist, it would be unexpected and quite surprising for the biological activity of a 14-β-H compound to resemble that of an otherwise identical 14-α-H compound. The stereochemistry at these centers has a dramatic effect on the molecular shape which, in my opinion, is expected by those of skill in the art to dramatically alter biological activity. In my opinion, the biological activity of a 14-β-H compound would not motivate one to synthesize corresponding 14-α-H compounds.

10. Furthermore, in my opinion, the chemical reactivity of a steroid compound is so dependent on the stereochemistry of the ring fusion centers that, to a steroid chemist, it would be unexpected and quite surprising for the reactivity of a 14-β-H compound to resemble that of an

otherwise identical 14-α-H compound. The stereochemistry at these centers has a dramatic effect on the molecular shape which, in my opinion, is expected to dramatically alter reactivity. In my opinion, the synthetic transformations of a 14-β-H compound would not be useful to predict how a corresponding 14-α-H compound would react, thus the synthetic methods taught by Scholz for 14-β-H compounds would not be expected to enable one to synthesize corresponding 14-α-H compounds.

11. The Examiner's second concern, as I understand it, is that Peeters teaches a broad genus that arguably encompasses some compounds of the present invention. The Examiner notes that R5 of the Peeters generic can be an optionally substituted acyl group, consistent with the structures of the present invention; thus the Examiner maintains that one of skill in the art would be motivated to select the acyl substituent for incorporation into a compound very analogous to those of the present invention, rendering it obvious.

12. It is my opinion that the compounds that Peeters exemplifies and enables differ from the present invention in the stereochemistry at C-17. Except for a single *intermediate*, the compounds described in Peeters all have a hydroxyl group as R5 on the Peeters generic, which would be called a β-hydroxy substituent. That intermediate (*see*, Example 5(b)-(c) in Peeters, at column 7, lines 56-62) lacks a second substituent at C-17, and further lacks the C-3 carbonyl of the present invention. The carbonyl on the A-ring in that compound is also protected as a dioxolane acetal; thus, that intermediate is <u>not</u> analogous to the claimed compounds of the present invention. In every compound described that contains both a hydroxyl and another substituent at C-17, the hydroxyl is β, *i.e.*, it is the R5 substituent, whereas the β substituent in the present invention is necessarily an acyl group, and a hydroxyl or other group in the claimed compounds can only be α.

13. Compounds of the present invention possess both an acyl substituent in the β (*beta*) position at C-17, *and* a hydroxy, alkoxy, acyloxy, or alkyl group in the α (*alpha*) position at C-17. In my opinion, the generic as drawn and the names of compounds set forth throughout the current application, which specify which substituent is α and which is β, would be clearly understood by those of skill in the art to place the acyl group at a position analogous to R5 in the Peeters generic (the β position), and the hydroxy, when present, at the corresponding R4 position (the α position). Clearly, in my opinion, the compounds exemplified by Peeters have the opposite (or inverted) stereochemistry at C-17 from the claimed compounds.

14. Moreover, the scope of the examples in Peeters is extremely narrow: the overall teaching offers very limited direction to one motivated to synthesize antiglucocorticoid compounds substantially different from the few described. The ***six*** novel compounds named and tested are all 17-$\beta$-hydroxy-17-$\alpha$-alkynes. It is not apparent, in my opinion, that one of skill in the art would foresee a "reasonable expectation of success" from such limited precedent in the synthesis of compounds where (a) the stereochemistry at C-17 is inverted, (b) an $sp^2$ carbon substituent is incorporated at C-17 in place of the sp-hybridized carbon of the alkyne group, and (c) a heteroatom (the carbonyl oxygen of the acyl group in the present invention) is introduced at the R5 substituent, simultaneously changing three features that were conserved in each of the compounds shown to possess the activity of interest in Peeters.

15. In my opinion, Peeters does not provide motivation to synthesize compounds like those of the present invention. Its preferred embodiments specify "$R_4$ is prop-1-ynyl, $R_5$ is hydroxy" (see Peeters, column 2 at line 53), which gives the opposite stereochemistry at C-17 from compounds that would be analogous to the compounds of the present invention. Other than including a generalized acyl group in a list of substituents that *could* be used for R5, and similarly including hydroxy in an array of substituents to be considered for R4, it gives no indication which substituents should stand out aside from that preferred embodiment description. Since the preferred compounds have the opposite stereochemistry from compounds analogous to the present invention, what little direction Peeters does provide ***teaches away*** from analogs that would render the present invention obvious, in my opinion, by teaching that the activity is associated with the opposite stereochemistry at C-17.

16. Tables 1 and 2 of the present application provide activity data showing the relative antiglucocorticoid and antiprogestational activities of selected compounds. Also, the following statement from page 144, lines 15-18 of the present application summarizes a key distinction of the present invention:

> Compounds 15, 38, 71, and 129 represent four of the most potent antiprogestational compounds known, and their low binding affinity for the glucocorticoid receptor would predict minimal antiglucocorticoid activity.

In my opinion, this data is surprising because it demonstrates that the antiglucocorticoid activity can be substantially separated from antiprogestational activity with the compounds of the present

invention. In Peeters, the compounds possessed very substantial antiglucocorticoid activity: that was the primary focus of the Peeters patent. The compounds of the present invention possess antiprogestational activity, with substantially less antiglucocorticoid activity. In my opinion, this is a highly significant separation of properties, because the reduced antiglucocorticoid activity greatly enhances the clinical potential for extended therapeutic applications.

17. Furthermore, Peeters only provides one synthesis route to create the stereochemistry at C-17 (*see* Example 5(d), column 8 at lines 7-21 of the Peeters patent). That example shows the addition of acetylene to a ketone at C-17, and it produces **quantitatively** the *beta*-hydroxy product, based on the yield reported. *Id.* The example provided began with 9.43 g of the ketone, with MW = 314, which amounts to 30.0 mmol of starting material, and produced 10.4 g of the acetylene addition product with MW = 340, which amounts to 30.6 mmol of product (102% of theoretical yield). There is no indication that the other isomer, which *might* be useful to prepare compounds of the present invention, was produced, and no other method to create a chiral tertiary alcohol center at C-17 is taught. All other examples of the synthesis of compounds with a carbon-based substituent at C-17 begin with the *beta*-hydroxy in the R5 position of the Peeters generic. Some involve modification of the acetylenic group, but in my opinion, none provides a way to invert that center or to introduce an acyl substituent at C-17.

18. Also, in our attempts to functionalize an acyl group at C-17 in the presence of the 11-β-dimethylaminophenyl group that is a preferred substituent in the present invention, we observed demethylation of the dimethylamino group rather than the desired functionalization of the acyl group. This has been published in *J. Chem. Soc. Chem. Commun.*, 1994, 1985-86, a copy of which is attached hereto as Exhibit B. The present invention required developing a new synthetic route for preparation of the claimed compounds. Thus, in my opinion, Peeters does not enable the synthesis of compounds of the present invention by one of ordinary skill in the art.

I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: August 2, 2002

Hyun K. Kim

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